CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-411

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

REMS MEMO – NEW APPROVAL TEMPLATE
October 21, 2009

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Psychiatry Products

NDA/BLA #s:	NDA 022411
PRODUCT:	Oleptro (trazodone hydrochloride) extended-release tablets
APPLICANT:	Labopharm Europe Limited
FROM:	Thomas Laughren, MD, DPP Division Director
DATE:	January, 2010

Section 505-1 of the Federal Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Oleptro (trazodone hydrochloride) extended-release tablets to ensure that the benefits of the drug outweigh the risk of suicidality in children, adolescents, and young adults, QT prolongation, and serotonin syndrome. In reaching this determination, we considered the following:

A. While it is not possible to estimate the size of the population likely to use Oleptro (trazodone hydrochloride) extended-release tablets for the indication of major depressive disorder (MDD), the prevalence of MDD for lifetime was 16.2% (32.6-35.1 million US adults) and for 12-month was 6.6% (13.1-14.2 million US adults) (Kessler et. al. 2003).

B. Oleptro (trazodone hydrochloride) extended-release tablets will be approved for the indication of treatment of MDD. MDD is a common disorder, widely distributed in the population, and usually associated with substantial symptom severity and role impairment. Patients with MDD have an increased risk of suicidality. MDD is also associated with marital, parental, social and vocational difficulties. Furthermore, MDD may complicate recovery from other medical illness.

C. Oleptro (trazodone hydrochloride) extended-release tablets have been shown to reduce the signs and symptoms of MDD in adult patients. With its demonstrated efficacy for MDD, Oleptro may reduce the disabling effects of MDD on the affected patients. The expected duration of therapy with Oleptro in patients who obtain a clinical response is likely to be 6 months to a year, and may be many years. MDD is considered a life-long disease, although the severity of symptoms may vary over time.

D. Known serious risks with use of Oleptro (trazodone hydrochloride) extended release tablets include: potential clinical worsening of suicidality risk in children, adolescents, and young adults, serotonin syndrome, and QT prolongation. Other serious risks listed in the label include precipitation of a manic/hypomanic episode, orthostatic hypotension and syncope, abnormal bleeding, interaction with MAOIs, priapism, hyponatremia, potential for cognitive and motor impairment, and discontinuation symptoms.

E. Oleptro (trazodone hydrochloride) extended release tablets is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, the FDA has determined that a Medication Guide is required for Oleptro (trazodone hydrochloride) extended release tablets. FDA has determined that Oleptro (trazodone hydrochloride) extended release tablets poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Oleptro (trazodone hydrochloride) extended release tablets. FDA has determined that Oleptro (trazodone hydrochloride) extended release tablets is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Oleptro (trazodone hydrochloride) extended release tablets, and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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/s/

WILLIAM H BENDER
01/14/2010

THOMAS P LAUGHREN
01/14/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 06, 2009
To:	Thomas Laughren, M.D., Director
	Division of Psychiatry Products (DPP)
Through:	Claudia Karwoski, PharmD, Director
	Division of Risk Management (DRISK)
	Jodi Duckhorn, MA, Team Leader
	Division of Risk Management
From:	LCDR Shawna Hutchins, RN, BSN
	Patient Labeling Reviewer
	Division of Risk Management
	Brian Gordon, MA
	Social Science Reviewer
	Division of Risk Management
Subject:	DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Oleptro™ (trazodone hydrochloride) Extended- Release Tablets
Application Type/Number:	NDA 22-411
Applicant/sponsor:	Labopharm Europe Limited
OSE RCM #:	2008-1552

1 INTRODUCTION

This memorandum is in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for OLEPTRO™ (trazodone hydrochloride). Please send these comments to the Applicant and request a response within two weeks of receipt. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. The Medication Guide is being reviewed by DRISK and will be provided under separate cover.

2 MATERIAL REVIEWED

- Proposed OLEPTRO™ (trazodone hydrochloride) Risk Evaluation and Mitigation Strategy (REMS) dated May 26, 2009
- OLEPTRO™ (trazodone hydrochloride) Risk Evaluation and Mitigation Strategy (REMS) supporting document, dated May 26, 2009

3 CONCLUSIONS AND RECOMMENDATIONS

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to Labopharm Europe Limited:

1. Revise your REMS goal as follows:

   The goal of this REMS is to inform patients about the serious risks associated with the use of OLEPTRO™ (trazodone hydrochloride) Extended- Release Tablets.

2. The Medication Guide distribution procedure does not provide sufficient details to determine whether it is in accordance with 21 CFR 208.24. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

   - A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
   - A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. We remind you of the requirement to comply with 21 CFR 208.24:

- A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

  "Dispense the enclosed Medication Guide to each patient." or

  "Dispense the accompanying Medication Guide to each patient."

4. The Timetable for Submission of Assessments of 18 months, 3 years, and 7 years is acceptable.
5. (b) (4) However the goal of the REMS is to inform patients about the serious risks associated with the use of OLEPTRO™ (trazodone hydrochloride). To adequately evaluate the goal of this REMS, you need to assess patients' understanding of the serious risks and safe use information contained in the OLEPTRO™ (trazodone hydrochloride) Medication Guide. The results should be included in the REMS assessment at 18 months, 3 years, and 7 years.

   - You should submit for review, 90 days prior to implementation, the methodology and instrument that will be used to evaluate patients' understanding about the safe use of OLEPTRO™ (trazodone hydrochloride). If you plan to conduct this assessment using a survey, the submission should include, but not be limited to:
     - Sample size and confidence associated with that sample size
     - How the sample will be determined (selection criteria)
     - The expected number of patients to be surveyed
     - How the participants will be recruited
     - How and how often the surveys will be administered
     - Explain controls used to minimize bias
     - Explain controls used to compensate for the limitations associated with the methodology
     - The survey instruments (questionnaires and/or moderator's guide).
     - Any background information on testing survey questions and correlation to the messages in the Medication Guide.
6. See the appended OLEPTRO™ (trazodone hydrochloride) REMS proposal for additional track changes.

Please let us know if you have any questions.

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/s/

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